DETAILED ACTION

Claims 7, 9, 12, 15 and 16 have been cancelled. Claims 17-28 are new. Claims 1-6, 8 and 11-, 13, 14 and 17-28 are under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 8/1/11 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Cho (US 5858398).

Cho discloses methods of making a pharmaceutical composition comprising admixing an active agent, where insulin is preferred but also calcitonins and other actives can be added, phosphorylcholines, which include phosphatidylcholine, a polyoxyethylene having 1-100 oxyethylene units, which reads on a polyol, as well as other components to produce a lamellar liquid crystalline phase of micelle for application to the dermal area of a patient (Claims 14, 15 and 1-3; column 9, lines 40-47; column 13, lines 3 and 22). Since the same exact materials are

combined by Cho as instantly claimed then the method must produce a multilamellar liquid crystalline carrier that entraps the insulin and stabilizes the insulin at room temperature. "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705,709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Consequently, instant claims 1, 17 and 20 are anticipated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Fanara et al. (WO 99/56725 and translated in US 6464987) as evidenced by Weder et al. (US 5726164) and the Phosal 50 PG data sheet 9/10/2007.

Fanara et al. disclose fluid pharmaceutical compositions for controlled release of at least one active substance comprising a therapeutically efficient amount of at least one active; 3 to 55 wt% of phospholipid; 16 to 72 wt% of one or several pharmaceutically acceptable solvents; and 4 to 52 wt% of at least one fatty acid that instantaneously gels in the presence of an aqueous phase (Abstract). Fanara et al. teach on page 10, Table 8, a composition by parts, which add up to 100 and so the Examiner understands this to be equivalent to wt%, with 74.70% Phosal 50 PG,

8.3% PEG 400; and 0.05% somatostatin, a polypeptide drug molecule, shown below with Examiner added emphasis:

Tableau 8 - Compositions Z_1 à Z_5 - Somatostatine (parties)

Composition	Z_1	Z_2	Z_3	Z_4	Z_5
Phosal 50 PG™	85	62,25	74,70	62,25	74,70
PEG 400	-	-	8,30	-	8,30
Propylène glycol	-	20,75	-	20,75	-
acide oléique	14,95	13	13	13	13
Somatostatine	0,05	0,05	0,05	0,05	0,05
tampon acétique	-	3,95	3,95	-	-
tampon acétique + lauryl sulfate de Na 7,5%	-	-	-	3,95	3,95

The data sheet on Phosal 50 PG states that Phosal 50 PG is phosphatidylcholine (PC) concentrate with at least 50% PC (lecithin) and propylene glycol, sunflower mono-diglyccrides and ascorbyl palmitate. Therefore, there is about (0.5 times 74.7) = 37.35% PC in the composition as a whole. Fanara et al. disclose methods of manufacturing the compositions by dissolving the phospholipids in solvent and incorporating the active substance into the mixture and optionally adding water and where the active substance is dissolved in a minimum amount of water before incorporation (claims 11 and 12).

The evidentiary reference of Weder et al. teaches that soybean lecithin is liquid crystalline at room temperature (column 7, lines 37-39).

Thus, the phosphatidylcholine of Fanara et al. is inherently a multilamellar liquid crystalline form at room temperature since unsaturated lipids are liquid crystalline at room temperature as taught by the evidentiary references. Since the components are the same as

instantly claimed then the composition is inherently multilamellar and entraps the somatostatin to stabilize it at room temperature and inherently is clear and delivers the polypeptide by transdermal delivery upon application of the composition to the skin. "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705,709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Also note Tables 9 and 10. Accordingly, instant claims 17 and 20 are anticipated. It is the Examiner's position that the step of dissolving the phospholipid in the solvent reads on "shaving the phosphatidylcholine into said polyglycol to form a phosphatidylcholine solution" and anticipates instant claim 18.

In addition, from the US Patent 6464987, Fanara et al. teach compositions with a ***therapeutically effective amount*** of an active substance such as a peptide active substance such as ***insulin***, calcitonin and somatostatin (claim 2; column 3, lines 42-65; column 7, lines 57-62 and column 8, example 8 and Table 16). If insulin is the only peptide present then the compostion would consist essentially of insulin. Fanara et al. teach the compositions with Phosal 50 PG TM which consists of 55.8% phosphatidylcholine, 1.9% of soybean fatty acids, 2.9% of sunflower monoglycerides, 1.9% of ethanol, 37.3% of propylene glycol and 0.2% of ascorbyl palmitate (Column 5, lines 55-59 and Tables 1-7, for example) and phosphatidylcholine from soybean (Column 6, lines 6-7 and column 9, lines 6-7 and Table 10 R4). Fanara et al. teach adding antioxidants such as ascorbyl palmitate (column 5, line 1). Fanara et al. teach that the compositions are in the form of emulsions, suspensions or oily preparations that have the property of gelling in the presence of an aqueous phase (Column 5, lines 18-26; and claims 1-18).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8 and 11, 13, 14 and 17-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (US 5,955,502) in view of Chaiyawat et al. (US 6,538,061) and Brieva et al. (US 5,985,298) and Francoeur et al. (US 5391548) and Szabo Anno et al. (US 5380761).

Applicant claims, for example:

> 1. (Previously presented) A method of formulating a topical insulin composition comprising:
>
> preparing a ~~non-liposome~~ phosphatidylcholine and polyglycol multilamellar liquid crystal ~~phosphatidylcholine non-polar~~ carrier for topical administration; and mixing an insulin solution into said carrier to entrap said insulin within said carrier, wherein said insulin is stabilized at room temperature.

Determination of the scope and content of the prior art (MPEP 2141.01)

Hansen et al. is directed to methods of administering an active substance in liquid crystalline phase to the skin of an animal such as a human (Abstract and claims 1-22). Hansen et al. teach a composition for use in the method in claims 1, 9, 16 and 18-21 (examiner added emphasis):

1. A method of using fatty acid esters as bioadhesive substances for administering substances selected from the group consisting of active substances, protective substances, and mixtures thereof, the method comprising applying a bioadhesive composition to the skin of an animal or human body, said bioadhesive composition comprising at least one substance selected from the group consisting of active substances, protective substances, and mixtures thereof, and at least 6% w/w, calculated on the composition, of at least one bioadhesive substance selected from the group consisting of fatty acid esters and mixtures of fatty acid esters, with the proviso that the bioadhesive composition is not in the form of a plaster.

9. A method to claim 1, wherein the fatty acid ester is selected from the group consisting of fatty acid esters of polyhydric alcohols, fatty acid esters of hydroxycarboxylic acids, fatty acid esters of monosaccharides, fatty acid esters of glyceryl-phosphate derivatives, fatty acid esters of glycerysulfate derivatives, and mixtures thereof.

16. A method according to claim 9, wherein the glycerylphosphate derivative is a phospholipid selected from the group consisting of phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositole, and diphosphatidylglycerol.

18. A method according to claim 9, wherein the fatty acid ester is selected from the group consisting of dioleoyl phosphatidylcholin, dilauroyl phosphatidylcholin, dimyristoyl phosphatidylcholin, dipalmitoyl phosphatidylcholin, distearoyl phosphatidylcholin, dibehenoyl phosphatidylcholin, dimyristoyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, dioleoyl phosphatidylglycerol, dilauroyl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dipalmitoyl phosphatidic acid and mixtures thereof.

19. A method according to claim 1, wherein said fatty acid ester or mixture of fatty acid esters forms a fluid crystalline phase when contacted with an aqueous medium.

20. A method according to claim 1, wherein contact of the composition with an aqueous medium results in formation of a fluid crystalline phase.

21. A method according to claim 1, wherein the composition further comprises a pharmaceutically acceptable excipient.

In claims 19 and 20, aqueous infers that water is present. ***Fluid crystalline phases and lamellar structures with lipid bilayers*** are taught which the Examiner interprets to read on multilamellar (column 6, lines 46-62). Hansen et al. teach active substances that are drugs including insulin, which would include and renders obvious human recombinant insulin prepared in 0.01 N HCl (column 9, line 59 through column 11, line 57; insulin at column 11, line 37). It is the Examiner's position that the active substance is intrinsically 'entrapped' in the phosphatidylcholine carrier in the absence of evidence to the contrary. *Hansen et al. teach that the composition may be formulated, hence prepared, according to conventional pharmaceutical practice (column 13, lines 43-45) and Hansen et al. teaches mixing the components (See Examples 1-9, for example).* Hansen et al. teach compositions containing **soybean oil and lecithin** (column 31, lines 23-30). Hansen et al. teach adding:

- parabens as preservative (column 15, line 1);

• PEG 200 and PEG 400 to the composition (column 15, line 29);

• lubricants (column 14, line 4);

• surfactants such as Tween (column 15, line 33-35); and

• other excipients such as antioxidants including ascorbic acid derivatives (column 13, line 35 through column 14, line 67).

Hansen et al. teach using from about 1% to about 90% w/w of the fatty acid ester in the composition (column 7, lines 40-52). Hansen teach using **soybean lecithin** which is inherently enriched with *polyenylphosphatidylcholine* (column 14, lines 60-64) (see instant specification [0013]). The amount of active substance is below about 10-15% w/w (column 11, lines 60-62) and includes **insulin** and other peptides such as **vasopressin** (column 11, lines 33-44). The method produces a room temperature stable clear composition in the absence of evidence to the contrary.

Chaiyawat et al. teach cosmetic compositions comprised of silicone fluids of low viscosity, less than 100 cSt at 25 °C, which exist as fluids at or near room temperature (Column 10, lines 48-59). The lubricious silicone fluids include polydimethylsiloxane polymers (dimethicone) (Column 10, lines 60-67 and Column 11, lines 1-4). Furthermore, Chaiyawat et al. teach that such compositions are suitable as hormone carriers (Column 12, lines 35-38 and 66) as well as drug delivery systems for topical administration of medicinal compositions to the skin (Column 12, lines 55-57). Chaiyawat et al. is relied upon for the teaching of adding polydimethylsiloxane lubricants to the composition.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190 (a surfactant), for improved long lasting adherence to the skin of cosmetics (Column 1,

lines 4-42; Column 3, lines 53-65). Brieva et al. is relied upon for teaching the addition of Dow 190 surfactant to the composition.

Szabo Anna et al. teach adding polyethyleneglycol 200-600 and preferably PEG 400 in liquid crystalline transdermal compositions (Abstract and column 2, lines 43-45).

Francoeur et al. teach transdermal pharmaceutical composition for treating diabetes, for example, and adding PEG 200 and PEG 400 to the compositions with preference to PEG 200 due to enhancement of transdermal flux (Abstract; title; column 17, Example 11; and column 19, lines 21-25).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02) 1.

1. The difference between the instant application and Hansen et al. is that Hansen et al. do not expressly teach method steps of preparing a phosphatidylcholine and polyglycol multilamellar liquid crystal carrier and mixing an insulin or vasopressin solution into the carrier to entrap the insulin/vasopressin and stabilize the insulin at room temperature. Hansen et al. do not expressly teach "shaving", "milling" or "sweeping" steps with the ingredients in the amounts instantly claimed. This deficiency in Hansen et al. is cured by the teachings of Chaiyawat et al., Brieva et al. Franceour et al., Szabo Anna et al. and the common sense of the ordinary artisan.

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the ingredients instantly claimed in the amounts instantly

claimed in the methods of Hansen et al., as suggested by Chaiyawat et al., Brieva et al. Franceour et al., Szabo Anna et al. and the common sense of the ordinary artisan, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Hansen et al. direct the artisan to combine the phosphatidylcholine with PEG200 and PEG400 and the art provides further rationale to select these specific PEGs for transdermal compositions as discussed above. Furthermore, the additional ingredients of siloxated polyether and polydimethylsiloxane are known components of topical compositions as taught by the art cited above. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

In addition, nothing unusual or unconventional about the instant method steps has been shown and therefore the instant method steps are considered obvious to the ordinary artisan and within the technical grasp of the ordinary artisan especially when Hansen et al. instruct the

artisan to use conventional methods to formulate the compositions. Thus warming the solutions to 40 C, mixing insulin for at least one hour at a concentration of 20 mg/ml, and milling and sweeping and shaving are all obvious means to prepare the solution in the absence of unexpected results. MPEP 2144.03 IV: "See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.)."

Consequently, combination of the instant ingredients in the method of preparing the composition of Hansen et al. is therefore merely the arbitrary selection of compounds well-known in the art as excipients for topical formulations and, therefore, requires no inventive effort by the ordinary artisan whatsoever absent unexpected results. The expected result is a topical composition comprising the active substance of Hansen et al.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8 and 11-, 13, 14 and 17-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grasela et al. (US 5837289) in view of Chaiyawat et al. (US 6,538,061) and Brieva et al. (US 5,985,298) and Francoeur et al. (US 5391548) and Szabo Anno et al. (US 5380761).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant claims, for example:

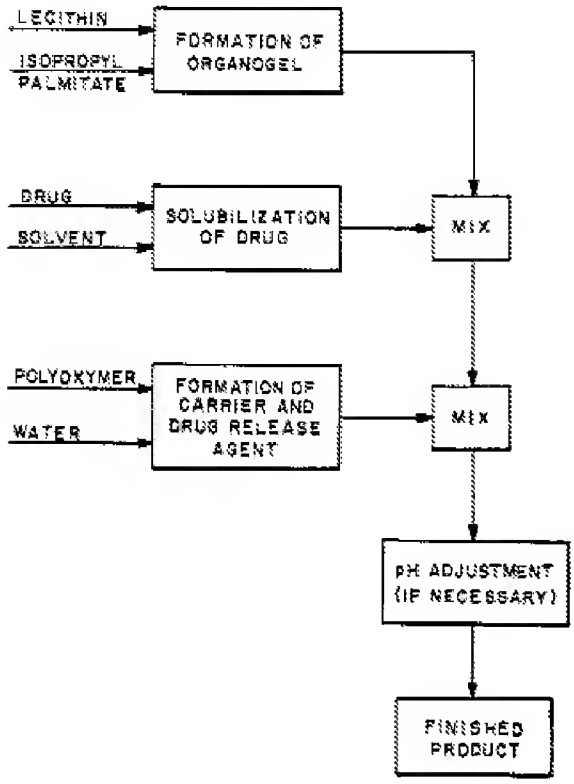
1. (Previously presented) A method of formulating a topical insulin composition comprising:

preparing a ~~non-liposome~~ phosphatidylcholine and polyglycol multilamellar liquid crystal ~~phosphatidylcholine non-polar~~ carrier for topical administration; and mixing an insulin solution into said carrier to entrap said insulin within said carrier, wherein said insulin is stabilized at room temperature.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Grasela et al. teaches methods of making transdermal lecithin organogels by blending solubilized medicine, organogel and polymeric component for application to a patients skin (Abstract; Figure 1; and claims 9-17). The single Figure shows a flowchart of a preferred embodiment:



Please note that the amount of each component is not limited in the method of Grasela et al. The lecithin is soya lecithin and soybean oil derived (column 6, lines 9-14 and column 17, example 1); the carrier can be water (column 6, line 29 and column 18, example 2); the medicine is insulin, which would include and render obvious human recombinant insulin prepared in 0.01 N HCl, or calcitonin (column 8, lines 29 and 44) and the amount of components can range from (column 16, lines 60-64):

- Medication <1%-20%
- Solvent for medication <1%-20%
- Organogel 20%-40%

- Carrier/release agent 40%-70%.

The phosphatidylcholine solution of Grasela et al. can be from **25%-75% soya lecithin** (column 17, Example 1) thus the organogel contains amounts of phosphatidylcholine instantly claimed. Polyoxyalkylene polymers are taught (claim 15). Grasela et al. teach warming the compositions until dissolution is complete (column 18, lines 1-3) as well as using a commercial mixer which reads on milling (column 18, lines 16-19). The method produces a room temperature stable clear composition in the absence of evidence to the contrary.

Chaiyawat et al. teach cosmetic compositions comprised of silicone fluids of low viscosity, less than 100 cSt at 25 °C, which exist as fluids at or near room temperature (Column 10, lines 48-59). The lubricious silicone fluids include polydimethylsiloxane polymers (dimethicone) (Column 10, lines 60-67 and Column 11, lines 1-4). Furthermore, Chaiyawat et al. teach that such compositions are suitable as hormone carriers (Column 12, lines 35-38 and 66) as well as drug delivery systems for topical administration of medicinal compositions to the skin (Column 12, lines 55-57) that contain preservatives (column 12, line 64). Chaiyawat et al. is relied upon for the teaching of adding polydimethylsiloxane lubricants and preservatives to the composition.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190 (a surfactant), for improved long lasting adherence to the skin of cosmetics (Column 1, lines 4-42; Column 3, lines 53-65). Brieva et al. teach adding preservatives such as methyl parabens to the composition (column 4, line 26 and Example 2). Brieva et al. is relied upon for teaching the addition of Dow 190 surfactant and methyl parabens to the composition.

Szabo Anna et al. teach adding polyethylene glycol 200-600 and preferably PEG 400 in liquid crystalline transdermal compositions (Abstract and column 2, lines 43-45).

Francoeur et al. teach transdermal pharmaceutical composition for treating diabetes, for example, and adding PEG 200 and PEG 400 to the compositions with preference to PEG 200 due to enhancement of transdermal flux (Abstract; title; column 17, Example 11; and column 19, lines 21-25).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Grasela et al. is that Grasela et al. do not expressly teach method steps of preparing a phosphatidylcholine and polyglycol multilamellar liquid crystal carrier and mixing an insulin or vasopressin solution into the carrier to entrap the insulin/vasopressin and stabilize the insulin at room temperature. Grasela et al. do not expressly teach "shaving", "milling" or "sweeping" steps with the ingredients in the amounts instantly claimed. This deficiency in Grasela et al. is cured by the teachings of Chaiyawat et al., Brieva et al. Franceour et al., Szabo Anna et al. and the common sense of the ordinary artisan.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the ingredients instantly claimed in the amounts instantly

claimed in the methods of Grasela et al., as suggested by Chaiyawat et al., Brieva et al. Franceour et al., Szabo Anna et al. and the common sense of the ordinary artisan, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the method of Grasela et al. is not limited to any specific amount of each component, thus it is merely routine optimization to come up with 45% w/w phosphatidylcholine or 53.25% w/w phosphatidylcholine, for example, and direct the artisan to combine the phosphatidylcholine with polyoxyalkylene polymers and the art provides further rationale to select PEG200 and PEG400 for transdermal compositions as discussed above. Furthermore, the additional ingredients of methyl parabens, siloxated polyether and polydimethylsiloxane are known components of topical compositions as taught by the art cited above. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

In addition, nothing unusual or unconventional about the instant method steps has been shown and therefore the instant method steps are considered obvious to the ordinary artisan and within the technical grasp of the ordinary artisan. Thus warming the solutions to 40 C, mixing insulin for at least one hour at a concentration of 20 mg/ml, and milling and sweeping and shaving are all obvious means to prepare the solution in the absence of unexpected results. MPEP 2144.03 IV: "See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.)."

Consequently, combination of the instant ingredients in the method of preparing the composition of Grasela et al. is therefore merely the arbitrary selection of compounds well-known in the art as excipients for topical formulations and, therefore, requires no inventive effort by the ordinary artisan whatsoever absent unexpected results. The expected result is a topical composition comprising the active substance of Grasel et al.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prescott (Methods in cell Biology 1976, volume 14 page 34) discloses that liposomes are simply the liquid-crystalline multi-lamellar structures obtained when phospholipids are dispersed in water.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/

Primary Examiner, Art Unit 1613